CLAIMS

We claim:

1. A double-stranded ribonucleic acid (dsRNA), comprising a complementary RNA strand and at least one lipophilic group, wherein the complementary RNA strand has a nucleotide sequence which is complementary to a target RNA, and wherein the target RNA is an mRNA transcript of a target gene or of a (+) strand RNA virus.

2. The dsRNA of claim 1, wherein the dsRNA further comprises a sense RNA strand, and wherein the lipophilic group is covalently attached to the complementary RNA strand or the sense RNA strand.

3. The dsRNA of claim 2, wherein the lipophilic group is covalently attached to a 5'-end of the complementary RNA strand or a 5'-end of the sense RNA strand.

4. The dsRNA of claim 3, wherein the lipophilic group is covalently attached to a 5'-end of the complementary RNA strand and the linkage between the lipophilic group and the 5'-end of the complementary RNA strand comprises a phosphodiester group.

5. The dsRNA of claim 3, wherein the lipophilic group is covalently attached to the 5'-end of the sense RNA strand.

6. The dsRNA of claim 5, wherein the linkage between the lipophilic group and the 5'-end of the sense RNA strand comprises a phosphodiester group.

7. The dsRNA of claim 5, wherein the lipophilic group is covalently attached to a 5'-end of the sense RNA strand and the linkage between the lipophilic group and the 5'-end of the sense RNA strand does not comprise a phosphodiester group.

8. The dsRNA of claim 1, wherein the complementary RNA strand comprises a 3'-end and a 5'-end, and wherein the 3'-end has a nucleotide overhang of 1 to 4 nucleotides.

9. The dsRNA of claim 1, wherein the complementary RNA strand comprises a 3'-end and a 5'-end, and wherein the 3'-end has a nucleotide overhang of 1 or 2 nucleotides.

10. The dsRNA of claim 1, wherein the dsRNA further comprises a sense RNA strand, wherein each of the complementary RNA strand and the sense RNA strand comprises a 3'-end and a 5'-end, wherein the lipophilic group is covalently attached to the 5'-end of the sense RNA strand, and wherein the 3'-end of the complementary RNA strand comprises a nucleotide overhang of 1 to 4 nucleotides.

11. The dsRNA of claim 10, wherein the linkage between the lipophilic group and the 5'-end of the sense strand does not comprise a phosphodiester group.

12. The dsRNA of claim 1, wherein the dsRNA is between 16 and 30 nucleotides in length.

13. The dsRNA of claim 1, wherein the dsRNA is between 16 and 25 nucleotides in length.

14. The dsRNA of claim 1, wherein the dsRNA is between 20 and 25 nucleotides in length.

15. The dsRNA of claim 1, wherein the lipophilic group is selected from the group consisting of an aromatic, aliphatic or alicyclic moiety, or a combination thereof.

16. The dsRNA of claim 1, wherein the lipophilic group is a steroid or a branched aliphatic hydrocarbon, or a combination thereof.

17. The dsRNA of claim 1, wherein the lipophilic group is a sterol.

18. The dsRNA of claim 13, wherein the sterol is cholesterol or a cholesterol derivative.

19. The dsRNA of claim 1, wherein the lipophilic group is cholesteryl (6-hydroxyhexyl) carbamate or 12-hydroxydodecanoic acid bisdecylamide.

20. The dsRNA of claim 1, wherein the target gene is expressed in a cell selected from the group consisting of a hepatocyte, a pancreatic cell, a uterine cell, a cell of a cervix, and a cell of a urinary bladder.

21. The dsRNA of claim 1, wherein the target gene is expressed in a liver cell selected from the group consisting of an endothelial cell, a Kupffer cell, and a parenchymal cell.

22. The dsRNA of claim 1, wherein the (+) strand RNA virus is a Hepatitis C Virus (HCV).

23. The dsRNA of claim 1, wherein the target gene is at least a portion of a 3'-untranslated region (3'-UTR) of a Hepatitis C Virus (HCV).

24. The dsRNA of claim 1, wherein the lipophilic group has a $\log K_{ow}$ exceeding 1.

25. The dsRNA of claim 1, wherein the lipophilic group has a $\log K_{ow}$ exceeding 1.5.

26. The dsRNA of claim 1, wherein the lipophilic group has a $\log K_{ow}$ exceeding 2.

27. The dsRNA of claim 1, wherein the lipophilic group has a $\log K_{ow}$ exceeding 3.

28. A pharmaceutical composition for inhibiting the expression of a target gene in a mammal, comprising:

a. a double-stranded ribonucleic acid (dsRNA) comprising a complementary RNA strand, wherein the complementary RNA strand has a nucleotide sequence which is complementary to an mRNA transcript of the target gene or of a (+) strand RNA virus, and a liphophilic group; and

b. a pharmaceutically acceptable carrier.

29. The pharmaceutical composition of claim 28, wherein the dsRNA further comprises a sense RNA strand, and wherein the lipophilic group is covalently attached to the complementary RNA strand or the sense RNA strand.

30. The pharmaceutical composition of claim 29, wherein the lipophilic group is covalently attached to a 5'-end of the complementary RNA strand and the linkage between the lipophilic group and the 5'-end of the complementary RNA strand comprises a phosphodiester group.

31. The pharmaceutical composition of claim 29, wherein the lipophilic group is covalently attached to a 5'-end of the sense RNA strand.

32. The pharmaceutical composition of claim 31, wherein the linkage between the lipophilic group and the 5'-end of the sense RNA strand comprises a phosphodiester group.

33. The pharmaceutical composition of claim 31, wherein the linkage between the lipophilic group and the 5'-end of the sense RNA strand does not comprise a phosphodiester group.

34. The pharmaceutical composition of claim 28, wherein the complementary RNA strand comprises a 3'-end and a 5'-end, and wherein the 3'-end has a nucleotide overhang of 1 to 4 nucleotides.

35. The pharmaceutical composition of claim 28, wherein the dsRNA further comprises a sense RNA strand, wherein each of the complementary RNA strand and the sense RNA strand comprises a 3'-end and a 5'-end, wherein the lipophilic group is covalently attached to the 5'-end of the sense RNA strand, and wherein the 3'-end of the complementary RNA strand comprises a nucleotide overhang of 1 to 4 nucleotides.

36. The pharmaceutical composition of claim 35, wherein the linkage between the lipophilic group and the 5'-end of the sense strand does not comprise a phosphodiester group.

37. The pharmaceutical composition of claim 28, wherein the dsRNA is between 16 and 30 nucleotides in length.

38. The pharmaceutical composition of claim 28, wherein the dsRNA is between 16 and 25 nucleotides in length.

39. The pharmaceutical composition of claim 28, wherein the dsRNA is between 20 and 25 nucleotides in length.

40. The pharmaceutical composition of claim 28, wherein the lipophilic group is selected from the group consisting of an aromatic, aliphatic or alicyclic moiety, or a combination thereof.

41. The pharmaceutical composition of claim 28, wherein the lipophilic group is a steroid or a branched aliphatic hydrocarbon, or a combination thereof.

42. The pharmaceutical composition of claim 28, wherein the lipophilic group is cholesteryl (6-hydroxyhexyl) carbamate or 12-hydroxydodecanoic acid bisdecylamide.

43. The pharmaceutical composition of claim 28, wherein the target gene is expressed in a cell selected from the group consisting of a hepatocyte, a pancreatic cell, a uterine cell, a cell of a cervix, and a cell of a urinary bladder.

44. The pharmaceutical composition of claim 28, wherein the target gene is a Hepatitis C Virus (HCV).

45. The pharmaceutical composition of claim 28, wherein the target gene is at least a portion of a 3'-untranslated region (3'-UTR) of a Hepatitis C Virus (HCV).

46. The pharmaceutical composition of claim 28, wherein the pharmaceutically acceptable carrier is an aqueous solution.

47. The pharmaceutical composition of claim 28, wherein the pharmaceutically acceptable carrier does not contain an agent that mediates the uptake of the dsRNA into a cell.

48. The pharmaceutical composition of claim 28, wherein the lipophilic group has a $\log K_{ow}$ exceeding 1.

49. The pharmaceutical composition of claim 28, wherein the lipophilic group has a $\log K_{ow}$ exceeding 1.5.

50. The pharmaceutical composition of claim 28, wherein the lipophilic group has a $\log K_{ow}$ exceeding 2.

51. The pharmaceutical composition of claim 28, wherein the lipophilic group has a $\log K_{ow}$ exceeding 3.

52. A method for inhibiting the expression of a target gene in a mammal, which comprises administering a pharmaceutical composition comprising a double-stranded ribonucleic acid (dsRNA) and a pharmaceutically acceptable carrier, wherein the dsRNA comprises a complementary RNA strand, wherein the complementary RNA strand has a nucleotide sequence which is complementary to an mRNA transcript of the target gene or of a (+) strand RNA virus, and a lipophilic group.

53. The method of claim 48, wherein the dsRNA further comprises a sense RNA strand, and wherein the lipophilic group is covalently attached to the complementary RNA strand or the sense RNA strand.

54. The method of claim 53, wherein the lipophilic group is covalently attached to a 5'-end of the complementary RNA strand and the linkage between the lipophilic group and the 5'-end of the complementary RNA strand comprises a phosphodiester group.

55. The method of claim 53, wherein the lipophilic group is covalently attached to a 5'-end of the sense RNA strand.

56. The method of claim 55, wherein the linkage between the lipophilic group and the 5'-end of the sense RNA strand comprises a phosphodiester group.

57. The method of claim 55, wherein the lipophilic group is covalently attached to a 5'-end of the sense RNA strand and the linkage between the lipophilic group and the 5'-end of the sense RNA strand does not comprise a phosphodiester group.

58. The method of claim 48, wherein the complementary RNA strand comprises a 3'-end and a 5'-end, and wherein the 3'-end has a nucleotide overhang of 1 to 4 nucleotides.

59. The method of claim 48, wherein the dsRNA further comprises a sense RNA strand, wherein each of the complementary RNA strand and the sense RNA strand comprises a 3'-end and a 5'-end, wherein the lipophilic group is covalently attached to the 5'-end of the sense RNA strand, and wherein the 3'-end of the complementary RNA strand comprises a nucleotide overhang of 1 to 4 nucleotides.

60. The method of claim 48, wherein the dsRNA is between 16 and 30 nucleotides in length.

61. The method of claim 48, wherein the dsRNA is between 16 and 25 nucleotides in length.

62. The method of claim 48, wherein the dsRNA is between 20 and 25 nucleotides in length.

63. The method of claim 48, wherein the lipophilic group is selected from the group consisting of an aromatic, aliphatic or alicyclic moiety, or a combination thereof.

64. The method of claim 48, wherein the lipophilic group is a steroid or a branched aliphatic hydrocarbon, or a combination thereof.

65. The method of claim 48, wherein the lipophilic group is cholesteryl (6-hydroxyhexyl) carbamate or 12-hydroxydodecanoic acid bisdecylamide.

66. The method of claim 48, wherein the target gene is expressed in a cell selected from the group consisting of a hepatocyte, a pancreatic cell, a uterine cell, a cell of a cervix, and a cell of a urinary bladder.

67. The method of claim 48, wherein the target gene is a Hepatitis C Virus (HCV).

68. The method of claim 48, wherein the target gene is at least a portion of a 3'-untranslated region (3'-UTR) of a Hepatitis C Virus (HCV).

69. The method of claim 48, wherein the pharmaceutically acceptable carrier is an aqueous solution.

70. The method of claim 48, wherein the pharmaceutically acceptable carrier does not contain an agent that mediates the uptake of the dsRNA into a cell.

71. The method of claim 48, wherein the lipophilic group has a $\log K_{ow}$ exceeding 1.

72. The method of claim 48, wherein the lipophilic group has a $\log K_{ow}$ exceeding 1.5.

73. The method of claim 48, wherein the lipophilic group has a $\log K_{ow}$ exceeding 2.

74. The method of claim 48, wherein the lipophilic group has a $\log K_{ow}$ exceeding 3.

75. A method for making a double-stranded ribonucleic acid (dsRNA), comprising the steps of:

a. preparing a first (complementary) RNA strand and a second (sense) RNA strand, wherein one of the RNA strands comprises a lipophilic group; and

b. mixing the first (complementary) RNA and the second (sense) RNA strands to form a dsRNA.

76. The method of claim 71, wherein the step of preparing the RNA strands comprises solid-phase synthesis in a 3' to 5' direction.

77. The method of claim 76, further comprising the step of attaching the lipophilic group to the first (complementary) or the second (sense) RNA strand, wherein the step comprises reacting a lipophilic molecule having a phosphoramidite group with a 5'-hydroxyl group of the first or the second RNA strand.

78. The method of claim 77, wherein the phosphoramidite group on the lipophilic molecule is formed by phosphitylation of a hydroxy group.

79. The method of claim 77, wherein the lipophilic molecule having a phosphoramidite group is formed by converting a cholesteryl chloroformate into an amide.

80. The method of claim 77, wherein the lipophilic molecule having a phosphoramidite group is formed by reacting a 12-hydroxylauric acid with a di-n-decylamine to form an amide.

81. The method of claim 77, wherein the lipophilic molecule having a phosphoramidite group is cholesteryl N-[6-(2-cyanoethoxy)-N,N-diisopropylaminophosphanyloxy]-hexyl carbamate or 12-[(2-cyanoethoxy) -N,N-diisopropylamino-phosphanyloxy]dodecanoic acid bisdecylamide.

82. The method of claim 77, wherein the lipophilic group has a $\log K_{ow}$ exceeding 1.

83. The method of claim 77, wherein the lipophilic group has a $\log K_{ow}$ exceeding 1.5.

84. The method of claim 77, wherein the lipophilic group has a $\log K_{ow}$ exceeding 2.

85. The method of claim 77, wherein the lipophilic group has a $\log K_{ow}$ exceeding 3.